

REVIEW



Management of cardiogenic shock: state-of-the-art

Christian Jung^{1,2*} , Raphael Romano Bruno¹, Marwan Jumean³, Susanna Price^{4,5}, Konstantin A. Krychtiuk⁶, Kollengode Ramanathan^{7,8}, Josef Dankiewicz⁹, John French^{10,11,12}, Clement Delmas^{13,14}, Alexandra-Arias Mendoza¹⁵, Holger Thiele¹⁶ and Sabri Soussi^{17,18}

© 2024 The Author(s)

Abstract

The management of cardiogenic shock is an ongoing challenge. Despite all efforts and tremendous use of resources, mortality remains high. Whilst reversing the underlying cause, restoring/maintaining organ perfusion and function are cornerstones of management. The presence of comorbidities and preexisting organ dysfunction increases management complexity, aiming to integrate the needs of vital organs in each individual patient. This review provides a comprehensive overview of contemporary literature regarding the definition and classification of cardiogenic shock, its pathophysiology, diagnosis, laboratory evaluation, and monitoring. Further, we distill the latest evidence in pharmacologic therapy and the use of mechanical circulatory support including recently published randomized-controlled trials as well as future directions of research, integrating this within an international group of authors to provide a global perspective. Finally, we explore the need for individualization, especially in the face of neutral randomized trials which may be related to a dilution of a potential benefit of an intervention (i.e., average effect) in this heterogeneous clinical syndrome, including the use of novel biomarkers, artificial intelligence, and machine learning approaches to identify specific endotypes of cardiogenic shock (i.e., subclasses with distinct underlying biological/molecular mechanisms) to support a more personalized medicine beyond the syndromic approach of cardiogenic shock.

Keywords: Cardiogenic shock, Intensive care, Myocardial infarction, Heart failure, Assist device, Outcome

Introduction

Cardiogenic shock (CS) is variably defined as a state of end-organ hypoperfusion due to the heart's inability to deliver sufficient oxygen to tissues to meet metabolic demands in the presence of adequate intravascular volume [1, 2]. Acute myocardial infarction-related cardiogenic shock (AMI-CS) was first alluded to over a century ago with description of groups of patients presenting with sudden obstruction of the coronary arteries. Patients in shock were described as “those cases in

which the attack is anginal, the pain severe, the shock profound and death follows in a few minutes or several minutes at the most” [3]. In 1942, Stead and Ebert described shock, or circulatory collapse, “as a result of a diminished venous return to the heart. It is characterized clinically by the signs of a marked decrease in cardiac output (CO) and tissue anoxia, namely, pallor, cold extremities, sweating, weak pulse, low arterial blood pressure, narrowing of the field of consciousness, and a normal or decreased venous pressure” [4]. With the exception of early invasive angiography and percutaneous coronary intervention (PCI) of the infarct-related artery in case of AMI-CS and the lack of substantial outcome effects using percutaneous mechanical circulatory support devices, there is only scarce evidence for other, frequently used interventions, such as the use of vasopressors and inotropic agents,

*Correspondence: Christian.jung@med.uni-duesseldorf.de

¹ Department of Cardiology, Pulmonology and Vascular Medicine, Heinrich-Heine-University Duesseldorf, Medical Faculty, Duesseldorf, Germany

Full author information is available at the end of the article

SHOUT
SHARE **IT**



fluid management, and general critical care interventions [5–7]. Despite a paucity of robust evidence, attempts to generate better data in recent years have been made. However, execution of high-quality randomized controlled trials (RCTs) in CS is hindered for numerous reasons including a heterogeneous patient population and clinical presentations, significant time pressure in recruitment, challenges in timely identification, and ethical and communication barriers [2, 8].

Definition of cardiogenic shock

The clinical definition of AMI-CS often used in clinical trials is a combination of low systolic blood pressure (SBP) of <90 mmHg and evidence of low CO (cardiac index [CI] of <2.2 L/min/m²) in patients with elevated filling pressures (pulmonary-capillary wedge pressure [PCWP] >15 mmHg) [5, 9]. The definition is scientifically pragmatic, as it relies on an SBP of less than 90 mmHg for a clinical diagnosis, and invasive hemodynamic assessment is not readily available on initial presentation. The Shock Academic Research Consortium (SHARC) consensus and the American Heart Association defined CS as cardiac disorder that results in both clinical and biochemical evidence of sustained tissue hypoperfusion [1]. Septic and hypovolemic shock also manifests with hypotension and end-organ hypoperfusion, and mixed forms of shock frequently exist simultaneously [2]. Certain patients have clear evidence of reduced CI and elevated PCWP but with an SBP greater than 90 mmHg. In addition to including absolute blood-pressure parameters in the definition of CS, the degree of hypotension relative to the patients preexisting blood pressure should be considered in the diagnosis of CS. In the SHOCK trial registry, 5.2% of patients were in CS but had an SBP >90 mmHg, and 7.1% had no evidence of organ hypoperfusion with an SBP <90 mmHg. Yet, both groups of patients had increased mortality [10]. While traditional criteria for CS are based on the presence of hypotension, recent consensus statements defined CS more broadly with the presence of hypoperfusion in patients without hypotension [2]. Normotensive CS phenotype, especially in young patients, are at high risk for significant hemodynamic deterioration and need a specific awareness [11].

The definition of CS including invasive hemodynamics was designated a class IIb, level of evidence B recommendation by the European Society of Cardiology (ESC), given the absence of prospective randomized data [12]. A consensus statement by the American Heart Association (AHA) supports invasive hemodynamic assessment in select circumstances, although it should not delay primary revascularization [13]. Proactive use of invasive hemodynamic monitoring should be considered early in the presentation of CS to guide management and

Take-home message

The management of cardiogenic shock is an ongoing challenge with high mortality rates. This review provides a comprehensive overview of contemporary management that includes pharmacologic therapy as well as the use of mechanical circulatory support and gives an outlook to support a more personalized medicine beyond the syndromic approach of cardiogenic shock.

risk prognostication [14]. However, recent RCTs did not require PCWP or other invasive hemodynamic measurements for diagnosis of CS [15–19].

Pathophysiology, clinical and hemodynamic phenotypes

The initiating event in CS is a significant alteration of cardiac function, with the resultant reduction in CO and elevation in filling pressures perpetuating myocardial ischemia, further exacerbated by reduction in aortic root pressure ultimately leading to impaired myocardial perfusion (increased left-ventricular pressure and decreased diastolic pressure). Compensatory vasoconstriction leads to coronary/systemic vascular bed dysfunction, potentially worsening myocardial and other organ ischemia [2]. CS can additionally precipitate a systemic inflammatory response, resulting in pathological peripheral vasodilation and altered microcirculation via release and activation of reactive oxygen species, pro-inflammatory cytokines, and activation of damage-associated molecular patterns. Therefore, beyond the traditional cardio-centric approach, CS is increasingly recognized as a systemic disease resulting in multi-organ dysfunction [20, 21]. These pathophysiological events are part of the downward spiral in CS. In the light of the fact that these events happen in a rapid sequence and stepwise worsen the prognosis [22], it is of paramount importance to therapeutically support the patient at the top of the CS spiral, rather than at the bottom to interrupt the chain of events. Importantly, the hallmark characteristic of heart failure-associated CS is congestion [23].

Heterogeneity of the CS clinical syndrome

Traditional approach: clinical/hemodynamic profiles

The traditional approach to CS classifies patients according to underlying etiology, timing (acute vs. acute-on-chronic), hemodynamic profile, and the extent of organ dysfunction [24]. CS related to AMI-CS now represents less than one-third of cases, with the majority related to acute decompensation in chronic heart failure [25]. As patients with chronic heart failure may have better-adapted compensatory mechanisms than those presenting with de novo pathology, the outcomes in these groups differ significantly [26]. Further, hemodynamic profiles vary widely with respect to CO, systemic vascular

resistance (SVR), and cardiac filling pressures, depending on the underlying pathology and acuity and different treatment strategies [2]. Most CS patients present with low CO with cold extremities, high SVR, and cardiac filling pressures. Patients with CS may also be euvolemic with a low CO; predominantly seen in acute-on-chronic heart failure. Vasodilatory CS is associated with a systemic inflammatory response and higher mortality risk [27]. Right-ventricular (RV) and biventricular dysfunction are associated with worse clinical outcomes when compared to isolated left-ventricular systolic dysfunction. The hemodynamics and ventricular/pulmonary involvement impact choice of monitoring and therapeutic strategies including the use of acute mechanical circulatory support (MCS) [24, 28].

Current/emerging approach: SCAI shock severity staging

The Society for Cardiovascular Angiography and Interventions (SCAI) cardiogenic shock (SCAI-CS) staging system was designed to provide a simple and standardized approach to classifying CS according to its severity, ranging from A-E [8]. Briefly, SCAI-CS stages are A (stable patients with acute cardiac conditions putting them at risk of CS), B (pre-shock with hypotension), C (classical shock with signs of hypoperfusion), D [deteriorating despite adequate initial supportive intervention(s)], and E (extreme shock). Numerous observational studies have confirmed the association between SCAI stage and mortality. Cardiac arrest constitutes a specific feature variable. An updated SCAI-CS staging system was subsequently published, recommending more in-depth phenotyping, including risk factors (largely unmodifiable), vasopressor/inotrope score, degree of metabolic derangement, acuity of onset, and uni-/biventricular pathology with/without pulmonary involvement [29]. Although a significant advance in stratification, several limitations to the SCAI staging exist, including that the classified severity can be highly dynamic, the response to interventions can be variable (beneficial/neutral/detrimental), and the timing of assessed/re-assessment lacks consensus, especially when considering its use for clinical trial inclusion criteria [30]. The SCAI classification does not encounter shock etiology nor age. It is also important to note that the conditions of CS change rapidly and that these temporal changes can hardly be reflected in a rigid classification. Another limitation of the SCAI classification is that multiple elements within the staging remain subject to variable interpretation.

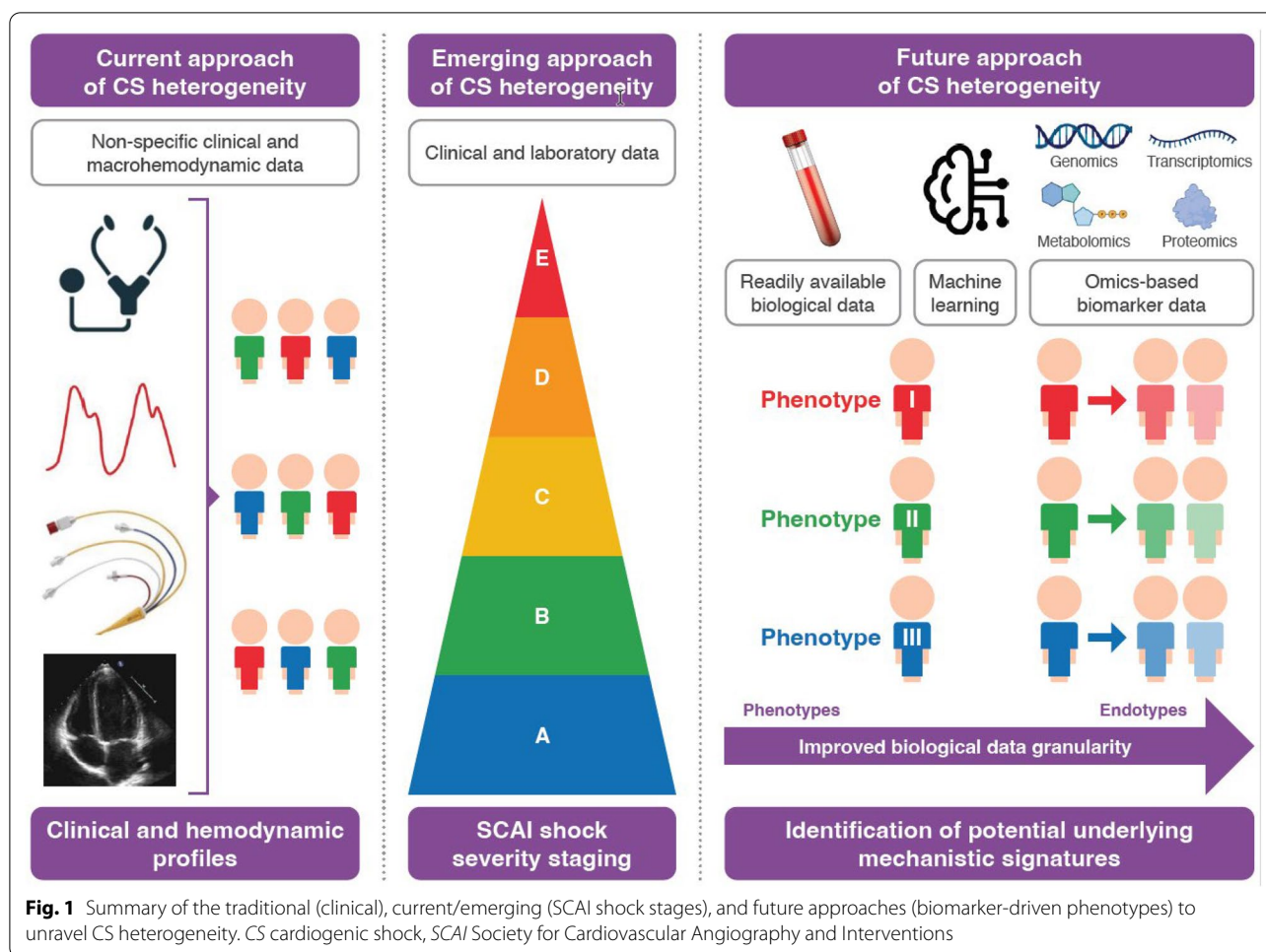
Future approach of CS: biological/biomarker-driven phenotypes

The clinical and severity approaches fail to fully address the underlying mechanistic signatures, impact of CS

biological heterogeneity, and the host response [31]. Recent research based on host-response biomarkers highlighted important molecular heterogeneity (i.e., inflammation, myocardial fibrosis, and endothelial dysfunction) within the spectrum of CS [32, 33]. Advances in artificial intelligence (AI) and machine learning are providing interesting avenues for the future; unsupervised machine learning (i.e., agnostic to outcome) identifies different classes in CS patients (“non-congested”, “cardiorenal”, and “cardiometabolic”) based on readily available laboratory data [34, 35] associated with early mortality independently from the SCAI classification [36]. Improved biological data granularity with omics-based biomarker together with AI may identify further CS phenotypes reflecting different underlying mechanistic signatures (i.e., endotypes), not apparent for the clinician at the bedside [37–40]. These endotypes may allow prognostic and predictive enrichment (i.e., identifying those patients most likely to benefit from a given intervention) and a biological fingerprint that may suggest personalized therapy, including immunomodulation [24, 40] and parallels the paradigm shift in critical care medicine overall, moving from syndromes, to an individualized patient approach (Fig. 1).

Diagnosis and laboratory evaluation

The diagnosis of CS should integrate findings from the presenting symptoms, physical examination, hemodynamic and laboratory parameters, as well as imaging modalities and be based on the definition provided above [29]. Laboratory evaluation of CS is mostly based on markers of tissue hypoperfusion and end-organ damage. Lactate represents the reference standard in laboratory assessment of tissue hypoperfusion and hypoxia [41, 42]. While rising lactate levels are associated with poor outcomes, the evidence for lactate clearance as a biomarker of outcome is less clear [43–46]. The tissue mismatch in oxygen demand and delivery in CS results in low oxygen saturations in blood returning to the heart which can be measured as mixed venous oxygen saturation (SvO₂) from the distal port of a pulmonary artery catheter (PAC) or as central venous oxygen saturation (ScvO₂) from a central venous catheter in the superior vena cava. Both SvO₂ and ScvO₂ are markers of oxygen delivery/consumption imbalance and thus indirectly of inadequate CO [47]. Arterio-venous difference in CO₂ from sampling of mixed/central venous and arterial blood may be also used to detect patients with inadequate CO (i.e., delta CO₂ ≥ 6 mmHg [48, 49]). However, the evidence to use this parameter is still limited. Arterial blood gas measurement provides further information and guidance on oxygenation and ventilation, acid-base disorders, electrolytes, and metabolic status.



In addition, biomarkers reflecting organ damage should be measured at least daily to detect and monitor damage in perfusion-sensitive organs. Daily measurement of serum creatinine together with urine output will aid in the detection of acute kidney injury [50] along with novel kidney biomarkers [51], if readily available. Patients with CS who suffer ischemic hepatitis have a poor prognosis. [52, 53]. Liver impairment can also be observed as congestive hepatopathy in CS. Natriuretic peptides (NT-proBNP) and markers of myocardial injury (cardiac troponins, see Table 1) may provide additional prognostic information in addition to underlying pathophysiology [15, 54, 55]. Complete blood count, standard metabolic panels, as well as coagulation laboratories need to be drawn frequently especially in patients treated with MCS.

Hemodynamic monitoring

Routine non-invasive (hemodynamic) monitoring for patients admitted with CS includes continuous electrocardiogram monitoring, pulse-oximetry, and monitoring of respiratory rate. Measurement of central venous

pressure, invasive arterial blood-pressure monitoring, and urine output are considered standard invasive monitoring in CS [2, 5]. Of potential interest is also the determination of end-tidal carbon dioxide (ETCO₂) in ventilated patient with CS indicative for impaired circulation and outcome [56]. PAC placement allows direct measurement of cardiopulmonary pressures and mixed venous saturation used for the calculation of vascular resistances and CI [16]. Routine use of PACs went out of vogue following no survival benefits demonstrated in RCTs—not specifically in CS—during the early 2000s, although inclusion and exclusion criteria of the relevant trials in the field are a matter of debate, as many of them excluded CS patients. However, with protocol-based management of CS becoming more standardized, it is becoming imperative that the use of PAC to derive cardiac power output (CPO) and pulmonary artery pressure index can stratify severity of shock early and guide advanced therapy in CS with improved clinical outcomes, leading to a resurgence in the use of such

Table 1 Overview of laboratory assessment and hemodynamic monitoring

Management	Comment	Frequency
Biomarkers		
Lactate	Marker of tissue hypoperfusion and hypoxia	As clinically indicated, at least every 4–8 h
ScvO ₂ /SvO ₂	Central venous/mixed venous oxygenation as a marker of inadequate oxygen delivery/consumption match	As clinically indicated, ideally at least every 8 h
Arterial blood gas analysis	Blood gases, oxygen saturation, blood pH, base excess, bicarbonate, electrolytes, lactate, electrolytes, hemoglobin, glucose	As clinically indicated, at least every 4–8 h
Serum creatinine	Marker of kidney perfusion and acute kidney injury, together with urine output and creatinine clearance	Daily
AST/ALT (GOT/GPT) INR	Marker of ischemic hepatitis	Daily
Complete blood count	Hemoglobin, white blood cell count, platelet count	At least once daily unless bleeding or having other complications
Coagulation parameters	PT, aPTT, thrombin time, fibrinogen, D-Dimer, INR, anti-Xa, pFhb	At least once daily unless need for therapeutic anticoagulation or on MCS treatment
Comprehensive metabolic panel	Blood sugar, electrolytes, Urea or BUN	At least once daily unless clinically indicated
Hemodynamic monitoring		
ECG monitoring		Continuous
Pulse-oximetry		Continuous
Respiratory rate		Continuous
Arterial blood pressure		Continuous
Central venous pressure		Continuous
Urine output		Continuous
Echocardiography	Bedside TTE / TOE for diagnostic purposes and cardiac output measurement based on LVOT VTI	At admission, every 24–48 h and when clinically indicated – for patients on MCS daily TTE should be considered
Non-invasive and minimally invasive cardiac output monitoring devices		Selective use
PAC		Selective but liberal use, repeated measures every 4–6 h

ScvO₂ central venous oxygen saturation, SvO₂ mixed venous saturation, AST aspartate transaminase, ALT alanine transaminase, GOT glutamic oxaloacetic transaminase, GPT glutamate pyruvate transaminase, PT prothrombin time, aPTT activated partial thromboplastin time, MCS mechanical circulatory support, ECG electrocardiogram, TTE transthoracic echocardiogram, TOE transesophageal echocardiogram, pulmonary artery catheter, LVOT left-ventricular outflow tract, VTI volume time integral, INR international normalized ratio, pFhb plasma free hemoglobin, PAC pulmonary artery catheter

monitors [2, 5, 17–19]. Furthermore, PAC repeated measures can give aid in the dynamic decongestion in CS [57]. It has been shown that the use of PAC in experienced hands is associated with improved outcomes. In addition, the quantification and potential pharmacological reduction of the systemic vascular resistance has a role in the management of CS patients. While a number of parameters can be derived from the PAC, CPO has strong diagnostic and prognostic values [58], and pulmonary artery pulsatility index (PAPi) helps further characterization of right heart function. Several minimally or non-invasive CO techniques are available, but evidence in favor of routine application is scarce [59]. In the hands of a trained clinician, transthoracic and transesophageal echocardiography (TTE and TOE) is not only a diagnostic tool but also a reliable, readily available, non-invasive modality to measure CO, its

changes [60, 61], and other parameters of cardiac function [62]. The application of echocardiography varies across centers in the light of the scarce evidence; however, the velocity time integral and its change over the treatment course in the left-ventricular outflow tract is a reliable tool to assess cardiac output [63].

Contemporary outcomes

As CS is a final common pathway for many acute and chronic cardiac pathologies, including AMI, myocarditis, valvular disease, acute decompensated heart failure, and arrhythmias, estimating both incidence and outcome is challenging. Typical surgical reasons for intra- or peri-operative CS that lead to (unplanned) extracorporeal life support (ECLS)-implant are isolated coronary artery bypass grafting (CABG), isolated valve surgery, thoracic aorta surgery, and a combination of CABG and valve surgery or other surgery leading to an intra-hospital

mortality of 63% [64]. In AMI-CS, mortality rates have been stable at around 40–50%, in both registry data and RCTs [65–71]. Although prior to reperfusion therapies mortality rates exceeded 80% [72]. A lack of uniformity of definitions, even among RCTs, further limits reliable analysis of temporal trends. However, there is likely an increasing incidence of acute decompensated heart failure-related CS (ADHF-CS) among patients with long-standing ventricular failure [73, 74]. As most RCTs have not included these patients, there is a paucity of data regarding both management and outcomes. Mortality rates appear to be similar to AMI-CS, but with longer hospital stays, a higher likelihood of need for biventricular support and tailored therapies [75, 76].

Causal treatment

Causal treatments aim at correcting the underlying pathology and include acute surgical or percutaneous valve interventions in, for example, acute aortic regurgitation in bacterial endocarditis or acute mitral regurgitation [77]. In most cases of CS, stabilization with vasopressors and inotropes while continuously assessing the need for MCS or heart transplantation remains the most common clinical strategy. In AMI-CS characterised by ischemia and profound depression of myocardial contractility, the therapeutic focus is on immediate revascularization [78]. This is based on the pivotal SHOCK trial [79] in which 6-month mortality was significantly reduced for patients who were randomized to early revascularization compared to standard care. In case of obvious revascularization indication such as ST-Segment Elevation Myocardial Infarction (STEMI) prehospital activation of PCI and also CS teams has potential to improve management. In the current ESC guidelines on acute coronary syndrome (ACS), this yields a 1B recommendation for immediate coronary angiography and PCI of the infarct-related artery or emergency coronary bypass grafting if PCI is not feasible [80]. Together with the recommendation for infarct-related artery (IRA)-only PCI during the index procedure, based on the CULPRIT-SHOCK trial, these are the only beneficial treatments recommended by guidelines based on RCT-level evidence. It seems that complete revascularization benefits do not outperform harm by increased procedural duration and contrast medium use in CS patients. Overall, treatment and (causal) management should be performed by a multidisciplinary team to plan the treatment and its order. Cardiogenic shock teams enhance early identification, phenotyping, and appropriate management, thereby improving outcomes in CS. [81]. Tavazzi et al. illustrated that CS management is heterogeneous and often not adherent to current recommendations [82] which could also be improved by dedicated teams [83].

Cardiac arrest

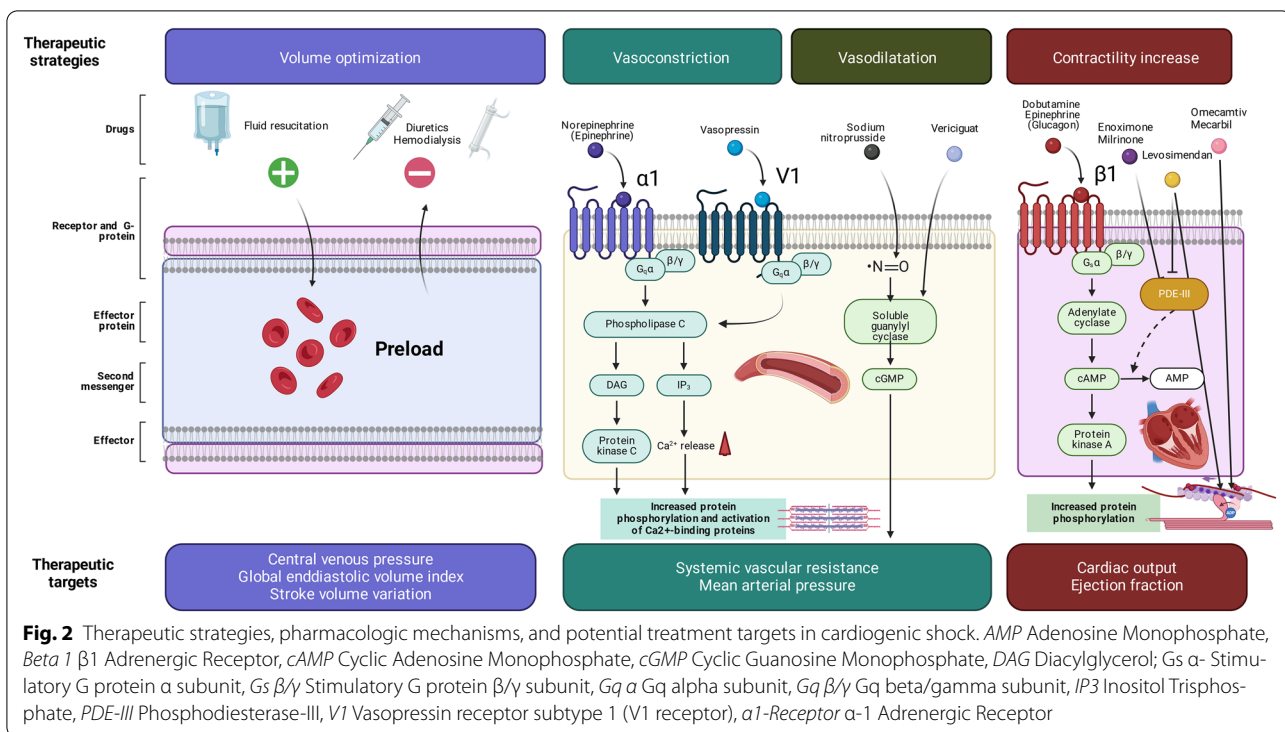
Cardiac arrest (CA) is the extreme stage of the spectrum in CS and concomitant CA with CS is common. Roughly half of all CS patients experience a CA before their hospitalization [84]. Conversely, CS is common after CA, due to a combination of the condition that caused the CA, and myocardial stunning due to global ischemia [85]. Data from CA studies on blood-pressure targets might offer some insights on vasopressor use in CS. There is a known correlation between vasopressor use and mortality in CS, but if there is a causative factor is unknown [86]. In patients without return of spontaneous circulation (ROSC), extracorporeal cardiopulmonary resuscitation (ECPR) implementation constitutes a treatment option helping stabilization of these patients [87] in selected patients. However, the current evidence is heterogeneous with a negative multicentre trial [87]. More trials and research are needed in this field.

Resource use

Costs associated with CS are spread over the cardiac catheterization laboratory, cardiac intensive care unit (CICU), and rehabilitation, while total healthcare burden has been poorly described. One European study described an average cost of 17,000 € per patient, mainly incurred by hospital-stay-related costs, implying a substantial societal cost. However, treatment had a low ratio of cost per life-year gained (9,632 €) [88]. Very high costs have also been confirmed in cohorts from North America [89], although the range is very wide: \$15,540–\$239,373 [90]. Of note, patients treated at centres with multidisciplinary CS shock teams had a shorter median intensive care unit (ICU) length of stay and were less frequently treated with mechanical ventilation or new renal replacement therapy, hence with lower treatments costs [91]. Considering the high resource use, management of CS in resource limited settings is even more challenging. However, implementation of protocolised management and other comparably cheap management tools can improve outcome and are possible in resource limited settings. Nevertheless, there is also evidence that advanced circulatory support programs can be successfully implemented in a limited resource country [92].

Pharmacologic management of CS

Pharmacologic management of CS (Fig. 2) can be divided into specific-causal and supportive drugs. Of note, not all drugs are available globally and their use is restricted to certain countries. In AMI-CS, for example, AMI is the causal trigger [80]. Drugs may help reducing the infarct area, and afterwards keeping the vessel open [93]. In AMI-CS, the myocardium not affected by the infarction



can be functional and compensatory hypercontractile. Acute inflammatory myocarditis might need immunosuppressive therapy. However, most cases of CS share some general aspects of supportive pharmacologic management of CS. Basically, stroke volume as key parameter in CS depends on preload, afterload, contractility, and heart rate. All these single factors can pharmacologically be influenced both in one direction or another. There is growing evidence from observational data that complete hemodynamic phenotyping might be associated with improved outcome in CS [94].

The most common way to optimize preload is fluid management (see Fig. 2, left part). Targeting pharmacological “decongestion” through enhanced salt and water excretion is a rational approach to improve outcomes and symptoms. Diuretics, by and promoting the excretion of water, sodium, and chloride, reduce ventricular filling pressures, fluid retention, and pulmonary edema in case of volume overload. Intravenous loop diuretics also induce rapid vasodilation, decreasing right atrial pressure and PCWP which had been associated with improved outcomes when the patient achieved euvolemic status [57], although high boluses carry the risk of reflex vasoconstriction. Intravenous loop diuretics (e.g., furosemide, bumetamide, or torsemide depending on local availability) are the most used diuretics in this context without any difference having been demonstrated between them to date in the context of acute heart failure. The use of

dual therapy or triple therapy by combining hydrochlorothiazide or acetazolamide and/or a mineralocorticoid receptor antagonist seems interesting to reduce congestion more quickly and effectively even if a transient deterioration in renal function is possible [95–97]. However, careful diuresis avoiding hypovolemia is crucial. Dynamic testing of preload sensitivity such as passive leg raising may help predict fluid responsiveness. When addressing central hypovolemia without congestion and improved hemodynamics following a leg raise test, crystalloid solutions are beneficial.

Afterload depends primarily on resistance vessels (arterioles, see Fig. 2 middle part) and left-ventricular wall stress. Vasopressors are the primary agents for stabilizing systemic vascular resistance by increasing blood pressure, aiming to enhance perfusion to vital organs—in CS particularly through raising diastolic pressure for improved coronary artery perfusion. The most commonly used vasopressor is norepinephrine (noradrenaline) [98], which is both recommended from the ESC and AHA [7], although a rather low level of evidence [2]. However, its use should be limited to the shortest duration and lowest dose, because escalating vasopressor requirement is linked to higher mortality in AMI-CS [99]—independently from the CPO [100–102]. Norepinephrine has vasoconstricting and inotropic effects [103]. Theoretically, this might lead to an increased left-ventricular afterload and myocardial oxygen consumption. Vasopressin

as alternative does not offer positive inotropic effects and might be associated with coronary vasoconstriction [104], but it might offer advantages in selected patients with pulmonary hypertension because of its lower effect on the pulmonary vascular resistance [105, 106]. Dopamine is not first-line therapy in many etiologies [107]. Left-ventricular afterload can be lowered by vasodilators especially in case of documented increased SVR (nitrates, nitroprusside sodium, and natriuretic peptides) that are commonly used in acute heart failure although there are no RCTs in CS and even though their handling and management are more difficult in CS context. Also, diuretics can effectively support decongestion management in case of hypervolemia.

Contractility can positively be modified using inotropes (see Fig. 2, right part), although their impact on the outcome remains a topic of ongoing debate. The choice of first-line inotropes currently used lacks a clear consensus [108]. There is no compelling evidence supporting the efficacy of any specific inotropic therapy in reducing mortality for hemodynamically unstable patients with CS, as neither the ESC nor the AHA guidelines make definitive recommendations, emphasizing the absence of robust evidence favouring one inotrope over another. In practical terms, the use of inotropes varies widely, and retrospective analyses indicate either higher mortality rates or no discernible positive effects associated with most inotropes [109, 110]. Individual choices should be made as a patient and disease tailored approach. While dobutamine is commonly used as the primary agent, levosimendan and phosphodiesterase (PDE)-III inhibitors might serve as an alternative or additional option when dobutamine proves ineffective, while conflicting data exists. Recent cochrane analyses found insufficient evidence to establish the superiority of any particular vasopressor or inotrope in terms of mortality [111]. Even though the 2016 ESC guidelines for heart failure recommended dobutamine as a “first line” inotrope, the current guidelines do not make specific recommendations [112, 113]. Observational studies and a recent RCT indicate favourable outcomes with dobutamine use in comparison to dopamine or epinephrine. Levosimendan, a calcium-sensitizer, increases cardiac inotropy and reduces afterload, demonstrating a long-lasting effect and potential benefits in catecholamine-refractory AMI-CS and other specific cases such as right heart failure [114, 115]. In addition, levosimendan might offer beneficial effects in patients with previous beta-blocker use [116].

Epinephrine and norepinephrine were compared in a small RCT and in large observational studies, and was shown to have a similar cardiac index evolution as primary efficacy outcome but higher incidence of refractory shock in the epinephrine group as main safety endpoint

[117]. However, the study included only 57 patients and the need for a PAC might have led to a selection-bias.

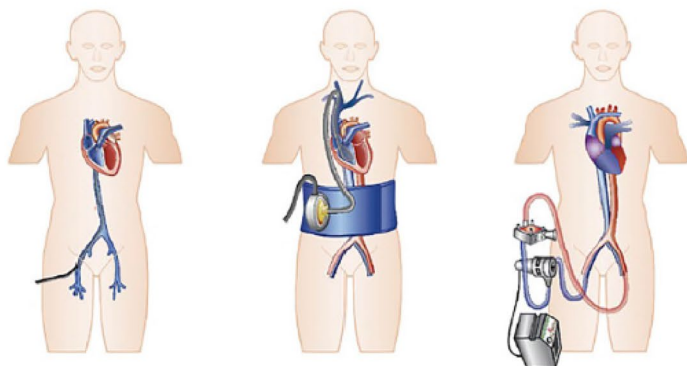
Selective PDE-III inhibitors, such as enoximone and milrinone, increase CO but lack consistent evidence supporting their use in critically ill patients except in specific cases such as pulmonary hypertension to also address right-ventricular contractility and afterload. The combination of PDE-III inhibitors with dobutamine may have a more pronounced positive inotropic effect, but caution is advised regarding potential synergistic vasodilatory effects when combining them or when combining with levosimendan. The recently published DOREMI trial found no difference between milrinone and dobutamine [118]. In consequence, the DOREMI trial gives no reason to change current practice to use dobutamine as first choice inotropic agent. Currently, LevoHeartShock (NCT04020263) investigates the effect of early use of levosimendan versus placebo on top of a conventional inotropic strategy in CS, while DOREMI-2 (NCT05267886) evaluates the impact of inodilators (milrinone/dobutamine) versus placebo with results being awaited [119]. In the future, more tailored pharmacological management approaches should be evaluated in clinical trials (Fig. 3).

Other general supportive pharmacological approaches include controlling the blood glucose level, providing adequate oxygen delivery, stress ulcer prophylaxis and early enteral feeding, as well as platelet inhibitors and anticoagulation. A comprehensive overview only focusing on pharmacologic treatment in CS has been published by Bruno et al. [105].

Mechanical circulatory support devices

Temporary mechanical circulatory support (tMCS, Figure 3) is a potential option for enhancing end-organ perfusion in patients with de novo or refractory CS [120]. It provides short-term hemodynamic intervention lasting from hours to weeks, is usually managed in a hub-and-spoke system available in tertiary centers, and is serving as a bridge-to-decision, bridge-to-recovery, bridge-to-LVAD (left-ventricular assist device), or bridge-to-transplantation. Various tMCS configurations offer partial or complete circulatory support, including percutaneous, surgical, and hybrid platforms with and without oxygenation. Multiple combinations like venoarterial extracorporeal membrane oxygenation (VA-ECMO; also called ECLS) with microaxial flow pumps (Impella®) which some call ECMella or ECPella, VA-ECMO with an intra-aortic balloon pump (IABP), BiPella (right- and left-ventricular microaxial flow pump), and left atrial-to-femoral artery support devices (TandemHeart™ or CentriMag™) with an left-ventricular (LV) Impella are feasible, addressing specific needs such as pulmonary support. tMCS

RIGHT HEART SUPPORT

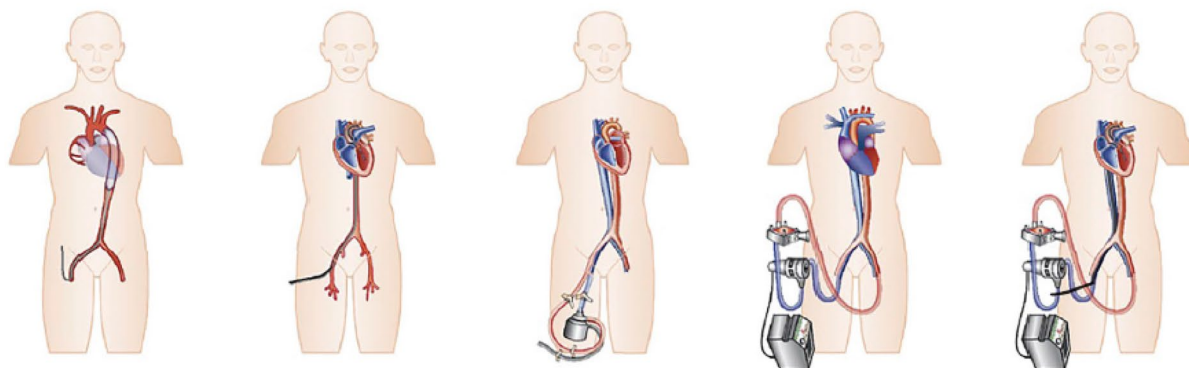


A. Impella RP (flex)

B. TandemHeart
RA-PA

C. VA-ECMO

LEFT HEART SUPPORT



A. IABP

B. Impella CP
Impella 5.5

C. TandemHeart

D. VA-ECMO

E. ECMELLA

	Size of the cannulae	Key contraindication / limitation	Ability to oxygenate blood	Recommended max. use - practical use may be much longer
Impella RP	22F	Mechanical tricuspid valve	No	14 days
TandemHeart RA-PA	16-31F	Mechanical tricuspid valve	Yes	14 days
VA-ECMO	15-25F	No suitable access site	Yes	14 days
IABP	7-8F	Severe aortic regurgitation	No	30 days
Impella CP / 5.5	CP: 14F 5.5: 21F	Mechanical aortic valve	No	10 days
TandemHeart	15-21 F	Moderate to Severe aortic regurgitation	Yes	14 days
VA-ECMO	15-25F	No suitable access site	Yes	14 days
ECMELLA	15-25F	Mechanical aortic valve	Yes	14 days

Fig. 3 Mechanical circulatory support devices. Right-ventricular (upper panel) and left-ventricular assist devices (lower panel). In biventricular failure assist, a combination of devices might be used. ECMELLA, the combination of VA-ECMO and Impella, serves as LV support and LV unloading strategy. RA right atrium, PA pulmonary artery, VA venoarterial (configuration), ECMO extracorporeal membrane oxygenation, IABP intra-aortic balloon pump, F French (1F = 0.33 mm), RV right-ventricular, LV left-ventricular

devices operate through distinct mechanisms, delivering diverse types and levels of hemodynamic support, each associated with specific potential complications. A thorough comprehension of each device's risk/benefit profile is paramount for determining its role in managing different stages and etiologies of CS [6]. Modern individualized therapy taking individual risks and benefits into account should still adhere to homogenous management plans which is an ongoing debate in CS, especially in the field of tMCS [121].

IABP has long deemed to provide some low degree of left-ventricular support by diastolic blood-pressure augmentation and afterload reduction, which, however, could not be confirmed in RCTs [122, 123]. Due to its ease of insertion, cost-effectiveness, and favorable adverse event profile, it has been widely used despite a lack of evidence. This electrocardiogram (ECG)-gated volume-displacement pump is percutaneously placed in the descending aorta, enhancing coronary perfusion during diastole, and reducing afterload during systole. In comparison to control, it was not able to significantly augment CO or any other hemodynamic variable in RCTs [122, 123]. Large-scale RCTs on IABP use in AMI-CS did not show survival benefits compared to medical therapy [67, 124]. Sufficient evidence for its benefit in other etiologies including acute or acute-on-chronic heart failure with CS and CS with mechanical complications post-AMI, possibly serving as a bridge-to-recovery or bridge-to-LVAD or heart transplantation, is not available [125].

The Impella family, with transvalvular axial flow pumps ranging from 3.5 to 5.5 L/min, has gained prominence in severe CS and LV-dysfunction. Newer devices like Impella 5.5 theoretically offer complete LV support, although RCTs demonstrating survival benefits in CS patients are lacking. Although overall evidence for Impella 5.5 is limited, its use grows along the advantages during longer support times and less access-site complications. Notably, two small RCTs, ISAR-SHOCK and IMPRESS-in-severe-shock, assessing Impella 2.5 and CP devices failed to show any survival benefit [126, 127]. Large-scale propensity matched studies encompassing more than 100,000 patients consistently showed no survival benefit or even higher mortality with consistent higher complication rates such as major bleeding and limb ischemia [128–133]. However, recently, the results of the Danish Germany (DanGer) shock trial [134] were published: in 360 highly selected patients with AMI-CS with anterior STEMI without high risk of hypoxic brain injury, comparing Impella® CP versus standard of care Impella support was associated with better 180-day outcome [135]. Despite the long recruitment period, the narrow inclusion criteria, and several open questions like the

highest ever reported increase in mortality from 30 days to 6 months in control patients, the shortest ICU time in the control arm, and the highest ever reported renal replacement therapy in the active tMCS arm, this RCT is an important study supporting the use of tMCS in selected patients.

The TandemHeart is a left atrial-to-femoral artery support device, delivering up to 4 L/min. Extracting blood directly from the left atrium effectively lowers PCWP and LV end-diastolic pressure. However, its retrograde arterial flow increases afterload during systole, resulting in minimal change or a slight decrease in myocardial oxygen consumption. Despite a study indicating no survival advantage over the IABP in managing AMI-CS [136, 137], the device holds potential value in specific cases requiring elevated CO support. This encompasses scenarios like mitral regurgitation, severe pulmonary hypertension, RV decompression, or when the Impella device is unsuitable, such as in severe aortic stenosis or the presence of a mechanical aortic valve. An added benefit is its capacity to incorporate an oxygenator into the arterial return circuit.

ProtekDuo is a dual-lumen cannula percutaneously inserted through the right internal jugular vein (IJV) to reach the pulmonary artery. Connected to an extracorporeal pump, it serves as a percutaneous right-ventricular assist device (RVAD). In patients experiencing RV failure, ProtekDuo offers isolated RV support and can deliver up to 5 L/min of flow, and an oxygenator can be integrated [138].

VA-ECMO, delivering flows of up to 6 L/min, can provide full respiratory and circulatory assistance. Peripheral VA-ECMO, the predominant configuration used, involves venous cannulation with a multi-stage cannula in the right atrium, directing blood to an extracorporeal pump and membrane oxygenator. Oxygenated blood is retrogradely pumped via the femoral artery into the descending aorta [139, 140]. Less-common central surgical configurations include cannulation in the right atrium or pulmonary artery, with return cannula placement in the ascending aorta. Additionally, the multi-stage venous cannula can be placed under fluoroscopic guidance in the left atrium across the inter-atrial septum thus draining both left and right atria combined to support the circulation while indirectly unloading the left ventricle as well (LAVA-ECMO). VA-ECMO is increasingly used in refractory CS and explored for ECPR [141]. The recent ECLS-SHOCK trial, involving AMI-CS, assessed early routine VA-ECMO alongside standard treatment. Results revealed no significant difference in 30-day all-cause death between groups (ECLS: 47.8%, control: 49%; relative risk [RR] 0.98, 95% confidence interval [CI] 0.80–1.19, $p=0.81$) [67]. Of note, these data are also in

line with the ECMO-CS trial [142]. This is further corroborated by an individual patient data meta-analysis of 4 RCTs which did not show a mortality benefit in AMICS with at the same time higher bleeding and peripheral ischemic complications [143]. In consequence and in the light of no benefits but relevant complications, the role of VA-ECMO in AMICS would be limited to patients with concomitant severe respiratory failure, biventricular failure, or cardiac arrest. If DanGer-Shock like patients may be the optimal candidates needs further evaluation. The use of ECMO with LV unloading remains to be ascertained [144].

tMCS device utilization in CS lacks standardized protocols, leading to varied practices [145]. The optimal timing for initiating and escalating tMCS devices including the optimal patient selection still remains undefined. tMCS are intended to offer hemodynamic support not to treat CS, and all devices offer variable hemodynamic support without addressing the etiology of CS. Thus, distinguishing the etiology (AMI vs. heart failure) may also be crucial. Recognizing hemodynamic instability, differentiating between univentricular and biventricular shock, and assessing respiratory failure for MCS device selection. Therefore, based on the current lack of evidence of a mortality reduction in RCTs, tMCS should be restrictively used based on advanced shock team decisions. Currently, a tMCS algorithm is not supported by evidence; however, potential selection steps have been proposed [146]. Ideally, tMCS is considered with CS and evidence of impaired stroke volume despite optimal pharmacologic support. Potentially, VA-ECMO should be selected in non-AMICS, AMICS with CA or biventricular failure, and Impella in isolated LV failure etiologies without cardiac arrest.

The clinicians should keep in mind the multiple issues that are specific to tMCS device assessment in RCTs: (i) it is challenging to completely standardize their use especially regarding the device management (e.g., anticoagulation strategy, specific settings, and clinician's experience). The example of the management of anticoagulation, antithrombotic therapy, and potential hemolysis—a major driver of adverse outcome—illustrates this effectively: treatment regimens differ widely contributing to ischemic events and bleeding and hence mortality in unexperienced hands; (ii) it is difficult to select the appropriate comparison with another device or combination of vasopressors/inotropes and the optimal timing of implementation; (iii) placebo-controlled device trials are impossible to design.

Future directions

Current management of CS is resource intensive and falls behind expectations with respect to outcomes.

Contemporary strategies see CS patients as a homogenous group with 'one size fits all' strategies and improvement efforts often fail in RCTs. From the clinical perspective, there is a large variety in patient presentations and responses to therapy. It seems prudent to classify patients in specific CS endotypes with subsequent treatment strategies. More efforts are needed to develop these endotypes bundles. AI and machine learning algorithms might facilitate these developments. To date, the treatment of the underlying etiology of CS such as PCI in AMI-CS is in most of the cases acceptable; however, the treatment of the sequelae remain challenging. An unmet need is the targeted therapy of the microcirculation, since it defines organ function and organ failure which subsequently defines outcome [147]. More efforts are needed to guide therapy to restore and maintain organ perfusion in the complex interplay with cardiac function and support as well as pharmacotherapy with all the challenges of fluid and perfusion pressure balancing. Early efforts that use optimal microcirculation as target need to get specific attention [148, 149]. This also goes in line with the identification of biomarkers and bioswitches, potentially identified using AI/machine learning approaches. Dipeptidyl peptidase 3 (DPP3) is an example that has been identified as an actionable biomarker (i.e., biological target); however, the next steps include the development as point-of-care diagnostics available at the bedside as well as identifying relevant mechanisms connected with the question whether this has the potential as therapeutic target. This approach may be incorporated in futures clinical trials that test the modulation of biotargets (e.g., anti-adrenomedullin and anti-DPP3 antibodies) in a preselected CS population (i.e., specific endotype [150–152]). Also, efforts need to be improved in multiple dimensions to balance the tip between positive and negative consequences in tMCS. It also remains an ongoing challenge to design the ideal tMCS trial not applying too broad or too narrow in- and exclusion criteria. Furthermore, future trials also need to address so far not well-represented patient groups, for example young SCAI D/E patients and non-AMICS patients with CS. At centre stage, there is the reduction in bleeding and peripheral ischemic events [153]. Improvements can be achieved in access-site management, anticoagulation, and the design of the devices. Correct management can also be improved by protocols and by qualification measures and seeing management of CS patient as multiprofessional and multidisciplinary team effort and as part of network organizations with potential transfer to expert centers. To move forward and addressing these questions, international trial networks should address these topics in streamlined strategies to power studies with relevant sample sizes in reasonable time frames.

Conclusions

Management of CS remains an ongoing challenge. Despite all efforts made on improving diagnosis and offering multimodal therapy, mortality remains high. More efforts are needed to identify the right therapy for the right CS patient needs more insight also in the light of comorbidities and metabolic demands [154]. Smaller sizes of MCS devices might also help to reduce negative side effects. Novel pharmacological substances might target the systemic syndrome CS. Innovative developments in biomarkers and use of artificial intelligence to assess trends might enhance personalized care in CS patients globally.

Author details

¹ Department of Cardiology, Pulmonology and Vascular Medicine, Heinrich-Heine-University Duesseldorf, Medical Faculty, Duesseldorf, Germany. ² Cardiovascular Research Institute Düsseldorf (CARID), Düsseldorf, Germany, Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany. ³ UTHealth McGovern Medical School, Houston, TX, USA. ⁴ Division of Heart, Lung and Critical Care, Royal Brompton Hospital, London, UK. ⁵ National Heart and Lung Institute, Imperial College London, London, UK. ⁶ Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria. ⁷ Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore, Singapore. ⁸ Cardiothoracic Intensive Care Unit, National University Heart Centre, National University Hospital, Singapore, Singapore. ⁹ Department of Clinical Sciences Lund, Lund University, Cardiology, Lund, Sweden. ¹⁰ Department of Cardiology, Liverpool Hospital, Sydney, Australia. ¹¹ School of Medicine, Western Sydney University, Sydney, Australia. ¹² South Western Sydney Clinical School, The University of New South Wales, Sydney, Australia. ¹³ Intensive Cardiac Care Unit, Cardiology Department, Toulouse University Hospital, Institute of Metabolic and Cardiovascular Diseases (I2MC), UMR-1048, National Institute of Health and Medical Research (INSERM), Toulouse, France. ¹⁴ REICATRA, Institut Saint Jacques, CHU de Toulouse, Toulouse, France. ¹⁵ Coronary Care Unit, Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico. ¹⁶ Department of Internal Medicine/Cardiology and Leipzig Heart Science, Heart Center Leipzig at University of Leipzig, Leipzig, Germany. ¹⁷ Department of Anesthesia and Pain Management, University Health Network (UHN), Women's College Hospital, University of Toronto, Toronto Western Hospital, Toronto, Canada. ¹⁸ University of Paris Cité, Inserm UMR-S 942, Cardiovascular Markers in Stress Conditions (MASCOT), Paris, France.

Funding

Open Access funding enabled and organized by Projekt DEAL.

Declarations

Conflict of interest

CJ reports institutional grants by the German research foundation, German ministry for economy and energy, State of Nordrhein-Westfalen, German space agency, European Union and Edwards Lifesciences as well as speaker fees outside the field of this article by Bristol Myers Squibb, Daiichi Sankyo and Boehringer-Ingelheim. RRB: no conflict of interest. MJ: no conflict of interest. SP: no conflict of interest. KAK reports speaker fees received from Daiichi Sankyo, Zoll Medical, Amarin, consulting fees by Amarin, Novartis, Sanofi and travel support provided by Amgen, Sanofi and Daiichi Sankyo. KR reports that he is the current Chair of Publications at the Extracorporeal Life Support Organisation. JD: no conflict of interest. JF: no conflict of interest. Clement Delmas reports lectures and consulting fees received by Abiomed and Abbott. A-AM: no conflict of interest. HT: no conflict of interest. SS: no conflict of interest.

Open Access

This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing,

adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 29 March 2024 Accepted: 18 August 2024

Published online: 10 September 2024

References

1. Waksman R et al (2023) Standardized definitions for cardiogenic shock research and mechanical circulatory support devices: scientific expert panel from the shock Academic Research Consortium (SHARC). *Circulation* 148(14):1113–1126
2. van Diepen S et al (2017) Contemporary management of cardiogenic shock: a scientific statement from the American heart association. *Circulation* 136(16):e232–e268
3. Herrick JB (1983) Clinical features of sudden obstruction of the coronary arteries. *JAMA* 250(13):1757–1762
4. Stead EA, Ebert RV (1942) Shock syndrome produced by failure of the heart. *Arch Inter Med* 69(3):369–383
5. Zeymer U et al (2020) Acute cardiovascular care association position statement for the diagnosis and treatment of patients with acute myocardial infarction complicated by cardiogenic shock: a document of the acute cardiovascular care association of the European Society of Cardiology. *Eur Heart J Acute Cardiovasc Care* 9(2):183–197
6. Thiele H et al (2019) Management of cardiogenic shock complicating myocardial infarction: an update 2019. *Eur Heart J* 40(32):2671–2683
7. McDonagh TA et al (2021) 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 42(36):3599–3726
8. Baran DA et al (2019) SCAI clinical expert consensus statement on the classification of cardiogenic shock: This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. *Catheter Cardiovasc Interv* 94(1):29–37
9. Califf RM, Bengtson JR (1994) Cardiogenic shock. *N Engl J Med* 330(24):1724–1730
10. Menon V et al (2000) Acute myocardial infarction complicated by systemic hypoperfusion without hypotension: report of the SHOCK trial registry. *Am J Med* 108(5):374–380
11. Delmas C et al (2019) Patients near to cardiogenic shock (CS) but without hypotension have similar prognosis when compared to patients with classic CS: is it time for redefine CS? A FRENDSHOCK multicenter registry analysis. *Arch Cardiovasc Dis Suppl* 11(1, Part 2):e301
12. Ibanez B et al (2018) 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 39(2):119–177
13. Henry TD et al (2021) Invasive management of acute myocardial infarction complicated by cardiogenic shock: a scientific statement from the American Heart Association. *Circulation* 143(15):e815–e829
14. Narang N et al (2023) Management of heart failure-related cardiogenic shock: practical Guidance for Clinicians. *Heart Fail* 11(7):845–851

15. Ceglarek U et al (2021) The novel cystatin C, lactate, interleukin-6, and N-terminal pro-B-type natriuretic peptide (CLIP)-based mortality risk score in cardiogenic shock after acute myocardial infarction. *Eur Heart J* 42(24):2344–2352
16. Bertaina M et al (2022) Pulmonary artery catheter monitoring in patients with cardiogenic shock: time for a reappraisal? *Card Fail Rev* 8:e15
17. Fang JC, Jones TL (2020) Can a pulmonary artery catheter improve outcomes in cardiogenic shock? *JACC Heart Fail* 8(11):914–916
18. Shah MR et al (2005) Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. *JAMA* 294(13):1664–1670
19. Garan AR et al (2020) Complete hemodynamic profiling with pulmonary artery catheters in cardiogenic shock is associated with lower in-hospital mortality. *JACC Heart Fail* 8(11):903–913
20. Bertini P, Guarracino F (2021) Pathophysiology of cardiogenic shock. *Curr Opin Crit Care* 27(4):409–415
21. Krychtiuk KA et al (2022) Basic mechanisms in cardiogenic shock: part 1-definition and pathophysiology. *Eur Heart J Acute Cardiovasc Care* 11(4):356–365
22. Hollenberg SM, Kavinsky CJ, Parrillo JE (1999) Cardiogenic shock. *Ann Intern Med* 131(1):47–59
23. Harjola VP et al (2018) Comprehensive in-hospital monitoring in acute heart failure: applications for clinical practice and future directions for research. A statement from the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 20(7):1081–1099
24. Sarma D, Jentzer JC, Soussi S (2023) Cardiogenic shock: a major challenge for the clinical trialist. *Curr Opin Crit Care*. <https://doi.org/10.1097/MCC.0000000000001066>
25. Berg DD et al (2019) Epidemiology of shock in contemporary cardiac intensive care units: data from the critical care cardiology trials network registry. *Circulation: Cardiovasc Qual Outcomes* 12(3): e005618
26. Bhatt AS et al (2021) De novo vs acute-on-chronic presentations of heart failure-related cardiogenic shock: insights from the critical care cardiology trials network registry. *J Cardiac Fail* 27(10):1073–1081
27. Jentzer JC et al (2020) Systemic inflammatory response syndrome is associated with increased mortality across the spectrum of shock severity in cardiac intensive care patients. *Circulation: Cardiovasc Qual Outcomes* 13(12): e006956
28. Burstein B et al (2022) Biventricular function and shock severity predict mortality in cardiac ICU patients. *Chest* 161(3):697–709
29. Naidu SS et al (2022) SCAI SHOCK Stage Classification Expert Consensus Update: A Review and Incorporation of Validation Studies: This statement was endorsed by the American College of Cardiology (ACC), American College of Emergency Physicians (ACEP), American Heart Association (AHA), European Society of Cardiology (ESC) Association for Acute Cardiovascular Care (ACVC), International Society for Heart and Lung Transplantation (ISHLT), Society of Critical Care Medicine (SCCM), and Society of Thoracic Surgeons (STS) in December 2021. *J Am Coll Cardiol* 79(9):933–946
30. Jentzer JC et al (2022) Advances in the staging and phenotyping of cardiogenic shock: part 1 of 2. *JACC Adv* 1(4):100120
31. Lawler PR, Mehra MR (2018) Advancing from a “hemodynamic model” to a “mechanistic disease-modifying model” of cardiogenic shock. *Elsevier*. 1285–1288
32. Soussi S et al (2023) Distinct host-response signatures in circulatory shock: a narrative review. *Intens Care Med* 38(1):50
33. Soussi S et al (2023) Clinical phenotypes of cardiogenic shock survivors: insights into late host responses and long-term outcomes. *ESC Heart Fail*. <https://doi.org/10.1002/ehf2.14596>
34. Zweck E et al (2021) Phenotyping cardiogenic shock. *J Am Heart Assoc* 10(14):e020085
35. Zweck E et al (2023) Clinical course of patients in cardiogenic shock stratified by phenotype. *JACC: Heart Fail* <https://doi.org/10.1016/j.jchf.2023.05.007>
36. Jentzer JC et al (2022) Validation of cardiogenic shock phenotypes in a mixed cardiac intensive care unit population. *Catheter Cardiovasc Interv* 99(4):1006–1014
37. Meijers WC et al (2021) Circulating heart failure biomarkers beyond natriuretic peptides: review from the Biomarker Study Group of the Heart Failure Association (HFA), European Society of Cardiology (ESC). *Eur J Heart Fail* 23(10):1610–1632
38. Soussi S et al (2021) Evaluation of biomarkers in critical care and perioperative medicine: a clinician's overview of traditional statistical methods and machine learning algorithms. *Anesthesiology* 134(1):15–25
39. Jentzer JC et al. (2022) Machine learning approaches for phenotyping in cardiogenic shock and critical illness: part 2 of 2. *JACC: Adv* 1(4): 100126
40. Mebazaa A, Soussi S (2023) Precision medicine in cardiogenic shock: we are almost there! 2023, American College of Cardiology Foundation Washington DC. p. 1316–1319
41. Vincent JL (2015) Serial blood lactate levels reflect both lactate production and clearance. *Crit Care Med* 43(6):e209
42. Fuernau G (2019) Lactate and other biomarkers as treatment target in cardiogenic shock. *Curr Opin Crit Care* 25(4):403–409
43. Fuernau G et al (2020) Arterial lactate in cardiogenic shock: prognostic value of clearance versus single values. *JACC Cardiovasc Interv* 13(19):2208–2216
44. Park IH et al (2021) Clinical significance of lactate clearance in patients with cardiogenic shock: results from the RESCUE registry. *J Intens Care* 9(1):63
45. Slottosch I et al (2017) Lactate and lactate clearance as valuable tool to evaluate ECMO therapy in cardiogenic shock. *J Crit Care* 42:35–41
46. Levy B et al (2024) Serial daily lactate levels association with 30-day outcome in cardiogenic shock patients treated with VA-ECMO: a post-hoc analysis of the HYPO-ECMO study. *Ann Intens Care* 14(1):43
47. Alkhouli M et al (2014) Clinical utility of central venous saturation for the calculation of cardiac index in cardiac patients. *J Card Fail* 20(10):716–722
48. McDonald CI et al (2021) Elevated venous to arterial carbon dioxide gap and anion gap are associated with poor outcome in cardiogenic shock requiring extracorporeal membrane oxygenation support. *ASAIO J* 67(3):263–269
49. Mathew R et al (2022) Optimal perfusion targets in cardiogenic shock. *JACC: Adv* 1(2): 100034
50. Koreny M et al (2002) Prognosis of patients who develop acute renal failure during the first 24 hours of cardiogenic shock after myocardial infarction. *Am J Med* 112(2):115–119
51. Fuernau G et al (2015) Prognostic impact of established and novel renal function biomarkers in myocardial infarction with cardiogenic shock: a biomarker substudy of the IABP-SHOCK II-trial. *Int J Cardiol* 191:159–166
52. Beer BN et al (2023) Incidence of hypoxic hepatitis in patients with cardiogenic shock and association with mortality. *Eur Heart J Acute Cardiovasc Care* 12(10):663–670
53. Jung C et al (2017) Incidence, laboratory detection and prognostic relevance of hypoxic hepatitis in cardiogenic shock. *Clin Res Cardiol* 106(5):341–349
54. Jarai R et al (2009) Early assessment of outcome in cardiogenic shock: relevance of plasma N-terminal pro-B-type natriuretic peptide and interleukin-6 levels. *Crit Care Med* 37(6):1837–1844
55. Schupp T et al (2023) Cardiac Troponin I but not N-Terminal Pro-B-Type natriuretic peptide predicts outcomes in cardiogenic shock. *J Pers Med* 13(9):1348
56. Aminiahdashti H et al (2018) Applications of End-Tidal Carbon Dioxide (ETCO₂) monitoring in emergency department; a narrative review. *Emerg (Tehran)* 6(1):e5
57. Ortega-Hernandez JA et al (2023) Dynamic invasive hemodynamic congestion profile impacts acute myocardial infarction complicated by cardiogenic shock outcomes: a real-world single-center study. *J Card Fail* 29(5):745–756
58. Lim HS (2020) Cardiac power output revisited. *Circulation: Heart Fail* 13(10): e007393
59. Arya VK, Al-Moustadi W, Dutta V (2022) Cardiac output monitoring - invasive and noninvasive. *Curr Opin Crit Care* 28(3):340–347
60. Mercado P et al (2017) Transthoracic echocardiography: an accurate and precise method for estimating cardiac output in the critically ill patient. *Crit Care* 21(1):136
61. Vieillard-Baron A et al (2019) A decade of progress in critical care echocardiography: a narrative review. *Intens Care Med* 45(6):770–788

62. Wong A, Chew M, Hernandez G (2023) Using ultrasound in ICU. *Intens Care Med* 49(5):563–565
63. Morales G et al (2022) Feasibility of very early identification of cardiogenic shock by semi-automated ultrasound exam in the emergency department. *Cureus* 14(10):e30927
64. Raffa GM et al (2017) In-hospital outcome of post-cardiotomy extracorporeal life support in adult patients: the 2007–2017 Maastricht experience. *Crit Care Resusc* 19(Suppl 1):53–61
65. Redfors B et al (2015) Angiographic findings and survival in patients undergoing coronary angiography due to sudden cardiac arrest in Western Sweden. *Resuscitation* 90:13–20
66. Thiele H et al (2013) Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *The Lancet* 382(9905):1638–1645
67. Thiele H et al (2023) Extracorporeal life support in infarct-related cardiogenic shock. *N Engl J Med* 389:1286–1297
68. Wayangankar SA et al (2016) Temporal trends and outcomes of patients undergoing percutaneous coronary interventions for cardiogenic shock in the setting of acute myocardial infarction: a report from the CathPCI Registry. *Cardiovasc Interv* 9(4):341–351
69. Babaev A et al (2005) Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA* 294(4):448–454
70. Peters EJ et al (2023) Characteristics, treatment strategies and outcome in cardiogenic shock complicating acute myocardial infarction: a contemporary Dutch Cohort. *J Clin Med* 12(16):5221
71. Lang CN et al (2021) Cardiogenic shock: incidence, survival and mechanical circulatory support usage 2007–2017-insights from a national registry. *Clin Res Cardiol* 110:1421–1430
72. Killip III T, Kimball JT (1967) Treatment of myocardial infarction in a coronary care unit: a two year experience with 250 patients. *Am J Cardiol* 20(4): 457–464
73. Bertaina M et al (2023) Differences between cardiogenic shock related to acute decompensated heart failure and acute myocardial infarction. *ESC Heart Fail* 10(6):3472–3482
74. Shah M et al (2018) Trends in mechanical circulatory support use and hospital mortality among patients with acute myocardial infarction and non-infarction related cardiogenic shock in the United States. *Clin Res Cardiol* 107:287–303
75. Tehrani BN et al (2020) A standardized and comprehensive approach to the management of cardiogenic shock. *Heart Fail* 8(11):879–891
76. Lim HS, Howell N (2018) Cardiogenic shock due to end-stage heart failure and acute myocardial infarction: characteristics and outcome of temporary mechanical circulatory support. *Shock* 50(2):167–172
77. Delgado V et al (2023) 2023 ESC Guidelines for the management of endocarditis: Developed by the task force on the management of endocarditis of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Nuclear Medicine (EANM). *Eur Heart J* 44(39):3948–4042
78. Bangalore S et al (2015) Outcomes with invasive vs conservative management of cardiogenic shock complicating acute myocardial infarction. *Am J Med* 128(6):601–608
79. Hochman JS et al (1999) Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *N Engl J Med* 341(9):625–634
80. Byrne RA et al (2023) 2023 ESC Guidelines for the management of acute coronary syndromes: Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J* 44(38):3720–3826
81. Herion FX et al (2023) Multidisciplinary cardiogenic shock team approach improves the long-term outcomes of patients suffering from refractory cardiogenic shock treated with short-term mechanical circulatory support. *Eur Heart J Acute Cardiovasc Care* 12(12):821–830
82. Van Edom CJ et al (2024) European practices on antithrombotic management during percutaneous mechanical circulatory support in adults: A survey of the Association for Acute CardioVascular Care (ACVC) of the ESC and the European branch of the Extracorporeal Life Support Organization (EuroELSO). *Eur Heart J Acute Cardiovasc Care*. <https://doi.org/10.1093/ehjacc/zuae040>
83. Tavazzi G et al (2022) Epidemiology, monitoring, and treatment strategy in cardiogenic shock. A multinational cross-sectional survey of ESC-acute cardiovascular care association research section. *Eur Heart J Acute Cardiovasc Care* 11(9):706–711
84. Thiele H et al (2012) Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 367(14):1287–1296
85. Ruiz-Bailén M et al (2005) Reversible myocardial dysfunction after cardiopulmonary resuscitation. *Resuscitation* 66(2):175–181
86. Thayer KL et al (2020) Invasive hemodynamic assessment and classification of in-hospital mortality risk among patients with cardiogenic shock. *Circulation: Heart Fail* 13(9): e007099
87. Suverein MM et al (2023) Early extracorporeal CPR for refractory out-of-hospital cardiac arrest. *N Engl J Med* 388(4):299–309
88. Collado E et al (2021) Hospitalization-related economic impact of patients with cardiogenic shock in a high-complexity reference centre. *Eur Heart J Acute Cardiovasc Care* 10(1):50–53
89. Miller PE et al (2022) Clinical outcomes and cost associated with an intravascular microaxial left ventricular assist device vs intra-aortic balloon pump in patients presenting with acute myocardial infarction complicated by cardiogenic shock. *JAMA Intern Med* 182(9):926–933
90. Malik A et al (2023) National trends for temporary mechanical circulatory support utilization in patients with cardiogenic shock from decompensated chronic heart failure: incidence, predictors, outcomes, and cost. *J Soc Cardiovasc Angiogr Interv* 2(6):101177
91. Papolos Alexander I et al (2021) Management and outcomes of cardiogenic shock in cardiac ICUs with versus without shock teams. *J Am Coll Cardiol* 78(13):1309–1317
92. Scolari FL et al (2022) Cardiogenic shock treated with temporary mechanical circulatory support in Brazil: The effect of learning curve. *Int J Artif Organs* 45(3):292–300
93. Ledwoch J et al (2017) Drug-eluting stents versus bare-metal stents in acute myocardial infarction with cardiogenic shock. *Heart* 103(15):1177–1184
94. Bertaina M et al (2022) Prognostic implications of pulmonary artery catheter monitoring in patients with cardiogenic shock: a systematic review and meta-analysis of observational studies. *J Crit Care* 69:154024
95. Mullens W et al (2022) Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med* 387(13):1185–1195
96. Trullàs JC, Casado J, Morales-Rull JL (2023) Combination diuretic therapy in acute heart failure. *Eur Heart J* 44(22):2047–2047
97. Mentz RJ et al (2023) Effect of torsemide vs furosemide after discharge on all-cause mortality in patients hospitalized with heart failure: the TRANSFORM-HF randomized clinical trial. *JAMA* 329(3):214–223
98. Kattan E, Ibarra-Estrada M, Jung C (2024) Knowing the ropes of vasopressor dosing: a focus on norepinephrine. *Intens Care Med*. <https://doi.org/10.1007/s00134-024-07374-y>
99. Lu X et al (2022) Norepinephrine use in cardiogenic shock patients is associated with increased 30 day mortality. *ESC Heart Fail* 9(3):1875–1883
100. Mebazaa A et al (2018) Management of cardiogenic shock complicating myocardial infarction. *Intens Care Med* 44(6):760–773
101. Jung C et al (2009) Acute microflow changes after stop and restart of intra-aortic balloon pump in cardiogenic shock. *Clin Res Cardiol* 98(8):469–475
102. Basir MB et al (2022) Vasopressors independently associated with mortality in acute myocardial infarction and cardiogenic shock. *Catheter Cardiovasc Interv* 99(3):650–657
103. Beurton A et al (2016) Beneficial effects of norepinephrine alone on cardiovascular function and tissue oxygenation in a pig model of cardiogenic shock. *Shock* 46(2):214–218
104. Asfar P, Radermacher P (2009) Vasopressin and ischaemic heart disease: more than coronary vasoconstriction? *Crit Care* 13(4):169
105. Bruno RR et al (2022) Pharmacological treatment of cardiogenic shock-A state of the art review. *Pharmacol Ther* 240:108230
106. Cleasby C et al (2023) The effect of vasopressin and hydrocortisone on cytokine trajectories. *Intens Care Med* 49(2):241–243
107. Chioncel O et al (2020) Epidemiology, pathophysiology and contemporary management of cardiogenic shock - a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 22(8):1315–1341

108. Scheeren TWL et al (2021) Current use of inotropes in circulatory shock. *Ann Intens Care* 11(1):21
109. Gao F, Zhang Y (2021) Inotrope use and intensive care unit mortality in patients with cardiogenic shock: an analysis of a large electronic intensive care unit database. *Front Cardiovasc Med* 8:696138
110. Karami M et al (2020) Vasopressors and inotropes in acute myocardial infarction related cardiogenic shock: a systematic review and meta-analysis. *J Clin Med* 9(7):2051
111. Uhlig K et al (2020) Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome. *Cochrane Database Syst Rev* 11(11): Cd009669
112. Ponikowski P et al (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 37(27):2129–2200
113. Authors/Task Force M et al. (2021) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*, 24(1): p. 4–131
114. Follath F et al (2002) Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet* 360(9328):196–202
115. Rokytá R, Pechman V (2006) The effects of Levosimendan on global haemodynamics in patients with cardiogenic shock. *Neuro Endocrinol Lett* 27(1–2): 121–7
116. Mebazaa A et al (2009) Levosimendan vs dobutamine: outcomes for acute heart failure patients on β -blockers in SURVIVE. *Eur J Heart Fail* 11(3):304–311
117. Levy B et al (2018) Epinephrine versus norepinephrine for cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol* 72(2):173–182
118. Mathew R et al (2021) Milrinone as compared with dobutamine in the treatment of cardiogenic shock. *N Engl J Med* 385(6):516–525
119. Parlow S et al (2023) Inotrope versus placebo therapy in cardiogenic shock: Rationale and study design of the CAPITAL DOREMI2 trial. *Am Heart J* 262:83–89
120. Pladet LC et al (2023) Prognostic models for mortality risk in patients requiring ECMO. *Intens Care Med* 49(2):131–141
121. Vandenbriele C, Tavazzi G, Price S (2023) Caution with conclusions and context of mechanical circulatory devices. *JAMA Intern Med* 183(3):277
122. Prondzinsky R et al (2010) Intra-aortic balloon counterpulsation in patients with acute myocardial infarction complicated by cardiogenic shock - the prospective, randomized IABP SHOCK Trial for attenuation of multi-organ dysfunction syndrome. *Crit Care Med* 38(1):152–160
123. Prondzinsky R et al (2012) Hemodynamic effects of intra-aortic balloon counterpulsation in patients with acute myocardial infarction complicated by cardiogenic shock: the prospective, randomized IABP shock trial. *Shock* 37(4):378–384
124. Thiele H et al (2013) Intraaortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock. Final 12-month results of the randomised IntraAortic Balloon Pump in cardiogenic shock II (IABP-SHOCK II) Trial. *Lancet* 382:1638–1645
125. den Uil CA et al (2009) Mechanical circulatory support devices improve tissue perfusion in patients with end-stage heart failure or cardiogenic shock. *J Heart Lung Transplant* 28(9):906–911
126. Seyfarth M et al (2008) A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *J Am Coll Cardiol* 52(19):1584–1588
127. Ouweneel DM et al (2017) Impella CP versus intra-aortic balloon pump support in acute myocardial infarction complicated by cardiogenic shock. The IMPRESS in Severe Shock trial. *J Am Coll Card* 69:278–287
128. Schrage B et al (2019) Impella support for acute myocardial infarction complicated by cardiogenic shock: a matched-pair IABP-SHOCK II trial 30-day mortality analysis. *Circulation* 139:1249–1258
129. Dhruva SS et al (2020) Association of use of intravascular microaxial left ventricular assist device vs intra-aortic balloon pump on in-hospital mortality and major bleeding among patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA* 323(8):734–745
130. Amin AP et al (2020) The evolving landscape of Impella use in the United States among patients undergoing percutaneous coronary intervention with mechanical circulatory support. *Circulation* 141(4):273–284
131. Almarzooq ZI et al (2023) Comparative effectiveness of percutaneous microaxial left ventricular assist device vs intra-aortic balloon pump or no mechanical circulatory support in patients with cardiogenic shock. *JAMA Cardiol*. <https://doi.org/10.1001/jamacardio.2023.1643>
132. Miller PE et al (2022) Clinical outcomes and cost associated with an intravascular microaxial left ventricular assist device vs intra-aortic balloon pump in patients presenting with acute myocardial infarction complicated by cardiogenic shock. *JAMA Intern Med* 182:926–933
133. Kim Y et al (2022) Outcomes of mechanical circulatory support for acute myocardial infarction complicated by cardiogenic shock. *Catheter Cardiovasc Interv* 99(3):658–663
134. Udesen NJ et al (2019) Rationale and design of DanGer shock: Danish-German cardiogenic shock trial. *Am Heart J* 214:60–68
135. Moller JE et al (2024) Microaxial flow pump or standard care in infarct-related cardiogenic shock. *N Engl J Med* 390(15):1382–1393
136. Thiele H et al (2017) Percutaneous short-term active mechanical support devices in cardiogenic shock: a systematic review and collaborative meta-analysis of randomized trials. *Eur Heart J* 38:3523–3531
137. Thiele H et al (2005) Randomized comparison of intraaortic balloon support versus a percutaneous left ventricular assist device in patients with revascularized acute myocardial infarction complicated by cardiogenic shock. *Eur Heart J* 26:1276–1283
138. Ravichandran AK et al (2018) Outcomes with the Tandem protek duo dual-lumen percutaneous right ventricular assist device. *ASAIO J* 64:570–572
139. Stephens AF et al (2023) ECMO PAL: using deep neural networks for survival prediction in venoarterial extracorporeal membrane oxygenation. *Intens Care Med* 49(9):1090–1099
140. Fernando SM et al (2023) Age and associated outcomes among patients receiving venoarterial extracorporeal membrane oxygenation—analysis of the Extracorporeal Life Support Organization registry. *Intens Care Med* 49(12):1456–1466
141. Low CJW et al (2024) Mechanical circulatory support for cardiogenic shock: a network meta-analysis of randomized controlled trials and propensity score-matched studies. *Intens Care Med* 50(2):209–221
142. Ostadal P et al (2023) Extracorporeal membrane oxygenation in the therapy of cardiogenic shock: Results of the ECMO-CS Randomized Clinical Trial. *Circulation* 147(6):454–464
143. Zeymer U et al (2023) Veno-arterial extracorporeal membrane oxygenation in patients with infarct-related cardiogenic shock - an individual patient data meta-analysis of randomised trials. *Lancet* 402(10410):1338–1346
144. Ling RR, Low CJW, Ramanathan K (2024) Mechanical left-ventricular unloading in extracorporeal cardiopulmonary resuscitation: a state of clinical equipoise. *Crit Care Med* 52(3):512–515
145. Basir MB et al (2019) Improved outcomes associated with the use of shock protocols: Updates from the National Cardiogenic Shock Initiative. *Cathet Cardiovasc Interv* 93(7):1173–1183
146. De Backer D et al (2024) Mechanical circulatory support in cardiogenic shock: microaxial flow pumps for all and VA-ECMO consigned to the museum? *Crit Care* 28(1):203
147. Merdji H et al (2023) Microcirculatory dysfunction in cardiogenic shock. *Ann Intens Care* 13(1):38
148. Bruno RR et al (2023) Direct assessment of microcirculation in shock: a randomized-controlled multicenter study. *Intens Care Med* 49(6):645–655
149. Tschollitsch T et al (2023) The value of clinical signs as indicators of shock. *Intens Care Med* 49(11):1413–1415
150. Buckel M et al (2023) Extending the 'host response' paradigm from sepsis to cardiogenic shock: evidence, limitations and opportunities. *Crit Care* 27(1):460
151. Laterre PF et al (2021) Safety and tolerability of non-neutralizing adre-nomedullin antibody adrecizumab (HAM8101) in septic shock patients: the AdrenOSS-2 phase 2a biomarker-guided trial. *Intens Care Med* 47(11):1284–1294

-
152. van Lier D et al (2022) Effects of enrichment strategies on outcome of adrenergic treatment in septic shock: Post-hoc analyses of the phase II adrenomedullin and outcome in septic shock 2 trial. *Front Med (Lausanne)* 9:1058235
 153. Helms J et al (2023) How to manage coagulopathies in critically ill patients. *Intens Care Med* 49(3):273–290
 154. Guidet B et al (2024) The trajectory of very old critically ill patients. *Intens Care Med* 50:181–194